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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Rec'd PCT/PTO 4 JAN 2005

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
1117WOORD01		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/050272	08.03.2004	10.03.2003

International Patent Classification (IPC) or national classification and IPC

C07D213/75

Applicant

ALTANA PHARMA AG

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.09.2004	01.02.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050272

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-21 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050272

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21

because:

☒ the said international application, or the said claims Nos. 21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050272

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	15-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the art

Reference is made to the following documents:

D1: WO 95/01338 A (BYK GULDEN LOMBERG CHEM FAB ; AMSCHLER HERMANN (DE)) 12 January 1995 (1995-01-12)

D2: WO 93/25517 A (CELLTECH LTD) 23 December 1993 (1993-12-23)

D3: COOK, D. C. ET AL.: "Process development of the PDE IV inhibitor 3-(cyclopentyloxy)-N-(3,5-dichlorpyrid-4-y l)-4-methoxybenzamide" ORGANIC PROCESS RESEARCH AND DEVELOPMENT, vol. 2, no. 3, 1998, pages 157-168, XP002247911

V-1. Novelty (Art. 33(2) PCT):

Claims 15 to 21 lack novelty. Roflumilast and its uses are known (see e. g. D1, in particular page 14 example 1). Even if the product prepared by the claimed process should differ in purity from the product disclosed in D1 these claims are not considered novel. It is the opinion of the ISA that, since purification techniques such as chromatography, distillation or recrystallisation are commonly known, the disclosure of a low molecular chemical compound is considered to make it available in **all levels of purity** unless there is evidence that until now all attempts

of purification by conventional techniques have failed. This does not appear to be the case here.

Process claims 1-14 are novel over D1 (example 1) because of the claimed ratio of the reagents and over D2 and D3 because these documents deal with piclamilast instead of roflumilast.

V-2. Inventive step (Art. 33(3) PCT)

Closest prior art for the process claims is seen in D1 (example 1 on page 14) since it deals with the synthesis of the same compound. The difference with respect to D1 is to use of the amino anion (1) in excess (cf. claim 1) with respect to the acid derivative (2) whereas in D1 substantially equimolar amounts are used. From D2 it is known that in analogous processes (preparation of piclamilast) the amine anion can be used in excess (cf. D2 examples 15 and 18). The claimed process must thus be seen as an obvious alternative of the process disclosed in D1.

The problem which is to be solved by the present application is the provision of an improved process for the preparation of roflumilast which does not lead to the formation of particular by-products (see page 2 of the description). The application contains comparative data (see table on page 10) which show that the claimed process shows some improvements with respect to a process known from D3 which was optimized for the synthesis of piclamilast. However, the process of D3 differs from the process disclosed in D1 not only in the different ratio of the starting materials but also in other parameters (e. g. the solvent). To show an unexpected improvement with respect to the closest prior art (i. e. example 1 of D1) comparative data would have to be submitted which differ only in the distinguishing feature, i. e. the molar ratio of the starting materials. In the absence of such data Art. 33(2) PCT is not fulfilled for claims 1-14.

Claims 15-21 are not novel and thus also not inventive.